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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/439,429	11/15/1999	CHRISTOPHER POWER	3045.00004	1631

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EXAMINER
EPPS, JANET L

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 12/16/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/439,429	Applicant(s) POWER ET AL.	
	Examiner Janet L Epps-Ford, Ph.D.	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 September 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Continued Prosecution Application

1. The request filed on 9-23-02 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/439,429 is acceptable and a CPA has been established. An action on the CPA follows.

Response to Amendment

2. Applicants have amended claim 5 to recite "at least one donor splice site" However, Applicants have not provided any support for this amendment. "[w]ith respect to newly added or amended claims, applicant should show support in the original disclosure for the new or amended claims." See MPEP §714.02 and § 2163.06 ("Applicant should * * * specifically point out the support for any amendments made to the disclosure."); and MPEP § 2163.04.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Priority

4. The first line of the specification recites that the instant application is a continuation of Application 08/176,862. However, the instant application is not a continuation of 08/176,862, the correct serial number is 09/176,862, now US Patent No. 6,046,319.

Claim Rejections - 35 USC § 112

5. Claims 5-6, and 9-12 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, for the reasons below and those of record set forth in the Official Action mailed 3-22-02.

Applicant's arguments filed 9-23-02 have been fully considered but they are not persuasive. Applicants traversed the instant rejection by way of amendment to more specifically cite both what is included in the antisense oligonucleotide and how this oligonucleotide results in the regulation of TNF-α expression. However, contrary to Applicant's assertions, claim 5, recites an antisense oligonucleotide comprising "an exon targeting an exon sequence of TNF-α that flanks at least one donor splice site." Claim 5 remains vague and indefinite since it is unclear if the antisense oligonucleotide comprises "an exon, targeting an exon sequence of TNF-α,"or if the antisense oligonucleotide merely comprises a sequence that targets "an exon sequence of TNF-α." Moreover, if the antisense oligonucleotide comprises an exon, it is unclear which exon Applicants are referring to, i.e. an exon of TNF-α or an exon from some other gene.

6. Claims 3-4, 7-10 and 13-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for inhibiting the expression of TNF-alpha *in vitro*, does not reasonably provide enablement for modulating, which includes for enhancing and inhibiting, the expression of TNF-alpha, *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims, for the reasons of record set forth in the Official Action mailed 11-02-2000.

Applicant's arguments filed 9-23-02 have been fully considered but they are not persuasive. Applicants traverse the instant rejection on the grounds that in the paper attached to Applicant's response, Applicants disclosed that the in vivo use of the method as set forth in the present application does perform as indicated in the in vitro studies. However, contrary to Applicant's assertions the experimental evidence provided in the cited paper by Applicants

utilizes methods that were not disclosed in the specification as filed. Furthermore, Applicants have not provided any information as to when and where the cited paper was published by Applicants. Moreover, if the cited reference was published after the filing date of the present application, the experimental data set forth in the cited reference can not be take as evidence of enablement since enablement is based upon the guidance given in the specification as filed, and the level of skill in the art at the time filing.

Additionally, the instant claims encompass treating a whole animal systemically, however the cited reference describes results associated with a method of locally treating hepatoma cells in the rat brain. As stated in the prior office action, the quantity of experimentation required to practice the invention as claimed would require determining modes of delivery in a whole organism such that a single gene is inhibited and the desired secondary effect (treating a patient with a disease associated with the expression of human tumor necrosis factor alpha) is obtained. The specification as originally filed provides no specific guidelines in this regard. The deficiencies in the specification would constitute undue experimentation since these steps must be achieved without instructions from the specification before one is enabled to practice the claimed invention.

Applicant's arguments alone cannot take the place of evidence in the record once an examiner has advanced a reasonable basis for questioning the disclosure. The instant claims remain rejected for the reasons of record.

Claim Rejections - 35 USC § 102

7. Claim 5 remains rejected under 35 U.S.C. 102(e) as being anticipated by Nyce et al., for the reasons of record set forth in the Official Action mailed 11-02-2000.

Applicant's arguments filed 9-23-02 have been fully considered but they are not persuasive. Applicants traverse the instant rejection on the grounds that "[W]hile targeting TNF-α is disclosed in column 3 of the patent, this is merely a laundry list of possible targets and there is no indication or suggestion in the specification as a whole for targeting TNF-α." Contrary to Applicant's assertions, although TNF-a is one gene target in a list of targets disclosed in Nyce et al., nevertheless antisense oligonucleotides targeting TNF-a are clearly anticipated by Nyce et al. Moreover, the term antisense oligonucleotide as per the teachings of Nyce et al., encompasses wherein the antisense oligonucleotides of their invention are preferably directed to an mRNA region of its target sequence containing a junction between intron and exon. Furthermore, Nyce et al. state that the antisense may either entirely overlie the junction or may be sufficiently close to the junction to inhibit splicing out of the intervening exon (col. 4, lines 55-65).

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claim 5 is rejected under 35 U.S.C. 102(b) as being anticipated by Taylor et al.

As stated above, the language of claim 5 is vague and indefinite as set forth above. For prior art purposes, the instant claim is interpreted as encompassing synthetic nuclease resistant

oligonucleotides targeting an exon sequence of TNF-alpha, or complementary to an exon sequence of TNF-alpha.

Taylor et al. discloses antisense oligonucleotides targeting an exon sequence of TNF-alpha mRNA, see Figure 2B (page 17447).

Taylor et al. teach each and every aspect of the instant invention thereby anticipating Applicant's claimed invention.

10. Claims 5 and 9 are rejected under 35 USC 102(b) as being anticipated by Sioud et al. (WO 94-10301 A1).

Claim 5 is interpreted as set forth in the above rejection. Claim 9 recites a pharmaceutical composition consisting of a ribozyme comprising a sequence complementary to at least a portion of exon sequences flanking donor splice sites in TNF-alpha, and a pharmaceutically physiologically acceptable carrier or diluent.

Sioud et al. disclose ribozymes comprising a sequence that is complementary to an exon sequence of TNF-alpha (see Figure 1A-1C). In another embodiment, Sioud et al. discloses compositions comprising said ribozymes and a pharmaceutically acceptable carrier (see pages 28-29).

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

12. Claim 5 is rejected under 35 U.S.C. 102(a) as being anticipated by Hartman et al. or Ojwang et al.

Hartman et al. (see page 631, Table 1, *Anti-TNF-in.*) and Ojwang et al. (page 1705, Table 1, T30797-T30800) disclose nuclease resistant antisense oligonucleotides comprising modifications and a sequence that is complementary to an exon sequence of TNF-alpha mRNA.

Hartman et al. and Ojwang et al. teach each and every aspect of the instant invention thereby anticipating Applicant's claimed invention.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L Epps-Ford, Ph.D. whose telephone number is 703-308-8883. The examiner can normally be reached on M-T, Thurs-Friday 9:00AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on (703)-308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-746-5143 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Janet L Epps-Ford, Ph.D.
Examiner
Art Unit 1635

JLE
December 12, 2002

SEAN McGARRY
PRIMARY EXAMINER